Integrated Risk Information System (IRIS) Public Science Meeting
June 29-30, 2016
Benzo[a]pyrene and *tert*-Butyl Alcohol

Science Topics

BaP Science Topic 1: Determining appropriate dose-metrics for expressing absorbed BaP dose.

The CAAC noted that both total mass of benzo[a]pyrene and mass per unit of skin area have been used as dose metrics in previous publications (Knafla et al., 2011; 2006; Hussain et al., 1998; LaGoy and Quirk; 1994; Sullivan et al., 1991), and that "there does not appear to be any empirical data available to inform a choice between these two dose metrics or to select another." Whichever dose metric is selected, it will need to be paired with an appropriate exposure equation for estimating an average daily dose of benzo[a]pyrene absorbed into human skin (an example equation can be found on p. G-14 of the supplemental information for the 2014 draft IRIS Benzo[a]pyrene assessment).

The IRIS Program is seeking public input on points that are important to consider and would be informative in selecting a dose metric.

BaP Science Topic 2: Modeling absorbed dose as a function of exposure parameters.

The CAAC noted that for the mouse study used to derive the dermal slope factor, applied dose closely approximates absorbed dose. The CAAC described conditions where this would be the case: the mass of the chemical is too small to cover completely the application area, the time between dose applications is long, and metabolism in the viable epidermis (the target tissue) is not saturated. In experimental studies where applied dose does not closely approximate absorbed dose, it would be important to estimate the absorbed dose from the exposure parameters in the study.

The CAAC also recommended that for subsequent use of the dermal slope factor to estimate the human cancer risk from an environmental exposure, the cancer risk should be estimated from the absorbed dose, and that the absorbed dose should be estimated from the exposure scenario.

Thus, there are recommendations to estimate absorbed dose both for an experimental exposure regimen in mice and for an environmental exposure scenario for humans.

The IRIS Program is seeking public input on factors to consider in developing a model of absorbed dose of benzo[a]pyrene as a function of the parameters of applied dose.

BaP Science Topic 3: Scaling absorbed dose between mouse skin and human skin.

After consideration of limitations in the available toxicokinetic data, EPA selected allometric scaling (i.e., body-weight3/4) and presented alternative approaches in the supplemental information for the 2014 draft IRIS benzo[a]pyrene assessment (see Appendix E). The CAAC noted that the science is uncertain for choosing the best approach for scaling absorbed dose from mouse skin to human skin. It is unknown whether whole-body toxicokinetics using allometric scaling is the most appropriate model within the skin compartment. The CAAC recommended consideration of thickness of the viable epidermis and metabolic rates in this tissue.

The IRIS Program is seeking public input on factors, with particular attention to quantitative factors, to better inform a scaling approach from mouse skin to human skin.

TBA Science Topic 2: Disentangling mechanisms of kidney toxicity and carcinogenicity

tert-Butanol is a metabolite of ethyl tertiary butyl ether (ETBE) and has been shown to mediate several kidney effects observed following ETBE exposure (Salazar et al., 2015), thus both chemical databases (i.e., *tert*-butanol and ETBE) provide information relevant to understanding the mechanisms underlying kidney toxicity and carcinogenicity. Reported effects following *tert*-butanol and ETBE exposure include changes in kidney weight, histopathological endpoints, and serum markers of kidney toxicity. α2u-Globulin was detected in the hyaline droplets of male rats following *tert*-butanol and ETBE exposure. While *tert*-butanol meets the criteria to indicate that an α2u-globulin process is operating and some of the kidney effects are not relevant to humans, the data were insufficient to conclude that α2u-globulin nephropathy is the sole contributor to *tert*-butanol-induced renal tumors; ETBE did not induce renal tumors. The observed renal effects in male and female rats following exposure to *tert*-butanol and ETBE are also associated with chronic progressive nephropathy (CPN). Several of the CPN pathological effects are similar to, and can obscure the lesions characteristic of, α2u-globulin-related hyaline droplet nephropathy (Webb et al., 1990). Additionally, CPN effects can be exacerbated by both chemical exposure as well as renal effects of α2u-globulin accumulation (U.S. EPA, 1991). The underlying mechanisms regulating CPN and its exacerbation are not well understood. For example, there is no scientific consensus on the role of CPN in rat kidney carcinogenesis (Melnick et al., 2012; Hard et al., 2013; Hard et al., 2009).

The public comment draft of the IRIS Toxicological Review for *tert*-butyl Alcohol (*tert*-Butanol) presents a summary of kidney toxicity and carcinogenicity evidence in Section 1.2.1 with additional discussion in Section 1.3.2. Because ETBE induces similar effects, all kidney evidence tables and figures from the Toxicological Review for ETBE are also being released to supplement the discussion.

The IRIS Program is seeking discussion on the roles that α2u-globulin nephropathy and CPN play in the observed kidney toxicity and carcinogenicity of tert-butanol.

TBA Science Topic 1: Mode of action for thyroid follicular cell tumors

Lifetime oral exposure to *tert*-butyl alcohol (*tert*-butanol) has been associated with increased thyroid follicular cell adenomas in female B6C3F1 mice and increased thyroid follicular cell adenomas and carcinomas in male B6C3F1 mice (NTP, 1995). An antithyroid MOA has been evaluated for the thyroid tumors observed following *tert*-butanol exposure in mice. This MOA involves increased clearance of thyroid hormones by the liver, which may cause continual secretion of TSH by the pituitary, leading to follicular cell hyperplasia and tumors (U.S. EPA, 1998a). EPA conducted an MOA analysis and found that the available database was inadequate to draw any conclusions regarding an antithyroid MOA.

The public comment draft of the Toxicological Review for *tert*-butyl Alcohol (*tert*-Butanol) discusses the synthesis of thyroid effects in Section 1.2.2. Further evaluation of carcinogenicity is provided in Section 1.3.2.

The IRIS Program is seeking public discussion on this or other possible modes of action and their relevance to the observed thyroid effects.